

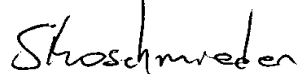
was taken up into ethyl acetate (2 ml) and to the solution was added a solution of hydrogen chloride in ethyl acetate (4N, 2 ml). The resulting precipitate was collected by filtration, washed with diisopropyl ether, and dried in vacuo to give 1-acetyl-4-(4-fluorophenylcarbonylmethyl)piperazine hydrochloride (1.47 g).

REMARKS

The specification has been amended to correct typographical or clerical errors. No new matter is believed to have been added by this amendment. An action on the merits and allowance of claims is solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Norman F. Oblon
Attorney of Record
Registration No. 24,618

Stefan U. Koschmieder, Ph.D.
Registration No. 50,238



22850

(703) 413-3000
Fax #: (703) 413-2220
NFO:SUK\la\smi

I:\atty\SUKOS\215869us-pr.wpd

Marked-Up Copy

Serial No: 09/926,641

Amendment Filed on:

3-14-02

IN THE CLAIMS

Claims 15-21 and 35 (Cancelled).

IN THE SPECIFICATION

Please delete line 17 on page 12 and replace with the following line.

--N-(1-cyclopropylcarbonylpiperidin-4-yl)-4-fluorobenzamide.--

Please delete the paragraph beginning on page 12, line 38 through page 13, line 5 and replace with the following paragraph.

--Suitable "lower alkenyl" and lower alkenyl moiety in the terms "lower alkenyloxy" and "lower alkenylamino" may be a straight or branched C₂-C₆ alkenyl such as ethenyl, propenyl, butenyl, pentenyl, hexenyl, isopropenyl, butadienyl, pentadienyl, hexadienyl or the like, in which preferable one is ethenyl, [propenyl] propenyl or butadienyl.--

Please replace the paragraph on page 17, lines 21-26 with the following paragraph.

--Suitable "acyl" may be carboxy; esterified carboxy; carbamoyl substituted with lower alkyl, aryl, [ar(lower)alkyl] ar(lower)alkyl, arylsulfonyl, lower alkylsulfonyl or a heterocyclic group; substituted or unsubstituted arylsulfonyl; lower alkylsulfonyl; cyclo(lower)alkylcarbonyl; lower alkanoyl; substituted or unsubstituted aroyl; a heterocycliccarbonyl and the like.--

Please C the paragraph on page 17, lines 27-38 with the following paragraph.

--The esterified carboxy may be substituted or unsubstituted lower alkoxy carbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, hexyloxycarbonyl, 2-iodoethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, etc.], substituted or unsubstituted aryloxycarbonyl [e.g. phenoxycarbonyl, 4-[nitrophenoxycarbonyl] nitrophenoxycarbonyl, 2-naphthyloxycarbonyl, etc.], substituted or unsubstituted ar(lower)alkoxy carbonyl [e.g. benzyloxycarbonyl, phenethyloxycarbonyl, benzhydryloxycarbonyl, 4-nitrobenzyloxycarbonyl, etc.], and the like, in which preferable one is unsubstituted lower alkoxy carbonyl and more preferable one is methoxycarbonyl or tert-butoxycarbonyl.--

Please replace the paragraph on page 19, lines 4-14 with the following paragraph.

--Suitable "N-protective group" may be common N-protective group such as substituted or unsubstituted lower alkanoyl [e.g. formyl, acetyl, propionyl, trifluoroacetyl, etc.], lower alkoxy carbonyl [e.g. tert-butoxycarbonyl, tert-amylloxycarbonyl, etc.], substituted or unsubstituted aralkyloxycarbonyl [e.g. benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.], 9-fluorenylmethoxycarbonyl, substituted or unsubstituted arenesulfonyl [e.g. benzenesulfonyl, tosyl, etc.], [nitrophenylsulfonyl] nitrophenylsulfonyl, aralkyl [e.g. trityl, benzyl, etc.] or the like, in which preferable one is lower alkoxy carbonyl and more preferable one is tert-butoxycarbonyl.--

Please replace the paragraph on page 21, lines 4-10 with the following paragraph.

--Another most preferred compound [II-2] is one selected from the group consisting of 1-acetyl-4-(4-[fluorophenylcarbonyl] fluorophenylcarbonyl)piperazine, 1-tert-butoxycarbonyl-4-(4-fluorophenylcarbonyl)piperazine, 1-(4-fluorophenylcarbonyl)-4-(4-trifluoromethoxybenzoyl)-piperazine and 1-methoxycarbonyl-4-(4-fluorophenylcarbonyl)piperazine.--

Please replace the paragraph on page 26, lines 10-14 with the following paragraph.

--Suitable "acid residue" may be halogen [e.g. [floro] fluoro, chloro, bromo, iodo], arenesulfonyloxy [e.g. benzenesulfonyloxy, tosyloxy, etc.], alkanesulfonyloxy [e.g. mesyloxy, ethansulfonyloxy, etc.], and the like, in which preferable one is halogen.--

Please replace the paragraph on page 30, lines 2-4 with the following paragraph.

--The object compound [II-1-g] [of] or its salt can be prepared by subjecting a compound [II-1-f] or its salt to elimination reaction of the N-protective group.--

Please replace the paragraph on page 31, lines 33-35 with the following paragraph.

--The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling [the] to heating.--

Please replace the paragraph on page 39, lines 7-20 with the following paragraph.

--The screening method of the present invention is preferably conducted under stimulation as mentioned above. Such stimulation is a model of a specific stimulation related to learning or tetanic stimulation. The stimulation is not particularly limited as long as the nerve cells present in the hippocampal slice are [exited] excited. Specific examples thereof include stimulation by potassium ion, electric stimulation, depolarization stimulation, stimulation with a drug and the like. When a mere addition of the test compound does not lead to the somatostatin release property and the test compound shows somatostatin release property only upon stimulation, it can be a confirmation that the nerve cells are free from influence of this test compound as long as no stimulation is involved, thus ensuring the safety of this compound.--

Please replace the paragraph on page 50, lines 17-23 with the following paragraph.

--To a stirred solution of 1-acetylpiperazine (0.648 g) in tetrahydrofuran (10 ml) was added 4-fluorophenyl isocyanate (0.574 g) at ambient temperature. After stirring at ambient

temperature for 1 hour, the solvent was removed by evaporation under reduced pressure, and the residue was triturated with diisopropyl ether to give 1-acetyl-4-(4-[fluorophenylcarbamoyl]fluorophenylcarbamoyl)piperazine (1.25 g).--

Please replace the paragraph on page 50, lines 28-31 with the following paragraph.

--The following compound was obtained by using 1-tert-butoxycarbonylpiperazine as a starting compound according to a similar manner to that of Reference example 2.

1-tert-Butoxycarbonyl-4-(4-[fluorophenylcarbamoyl]fluorophenylcarbamoyl)piperazine--

Please replace the paragraph on page 51, lines 16-27 with the following paragraph.

--To a suspension of 1-acetyl-4-aminopiperidine hydrochloride (0.4 mg) in dichloromethane (5 ml) were added in turn pyridine (0.54 ml) and 4-fluorophenyl chloroformate (0.29 ml) at 0°C. The mixture was allowed to warm to ambient temperature and stirred for 1 hour, which was taken up into a mixture of water and ethyl acetate. The separated layer was washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate, and brine and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue which was titrated with diisopropyl ether to give 1-acetyl-(4-fluorophenoxycarbonyl-amino)piperidine [1-acetyl-(4-fluorophenoxycarbonyl-amino)piperidine](347 mg).--

Please replace the paragraph beginning on page 52, line 38 through page 53, line 12 with the following paragraph.

--To a suspension of 1-acetyl-4-aminopiperidine hydrochloride (715 mg) in dichloromethane (7 ml) were added diisopropylethylamine (1.83 ml) and a solution of 4-fluorobenzenesulfonyl chloride (0.83 mg) in dichloromethane (2 ml) at [amibient] ambient temperature. After stirring for 6.5 hours, the reaction mixture was diluted with

dichloromethane and washed with water, saturated aqueous sodium hydrogen carbonate, and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. A residue was purified by column chromatography (silica gel 50 ml, dichloromethane:methanol = 50:1 to 20:1). After rinse with diisopropyl ether, N-(1-acetylpiperidin-4-yl)-4-fluorobenzenesulfonamide (859 mg) was obtained.--

Please replace the paragraph beginning on page 54, lines 4-14 with the following paragraph.

--To a suspension of 1-acetyl-4-aminopiperidine hydrochloride (536 mg) in dichloromethane (5 ml) were added 4-[~~florophenyl~~]fluorophenyl isocyanate (375 μ l) and diisopropylethylamine (575 μ l) at ambient temperature. After stirring for 3 hours, the reaction mixture was diluted with dichloromethane. An organic phase was separated and an aqueous phase was extracted with dichloromethane. A combined organic phase was dried over magnesium sulfate and the solvents were removed under reduced pressure. After crystallization from diisopropyl ether and n-hexane, N-(1-acetylpiperidin-4-yl)-N'-(4-fluorophenyl)urea (448 mg) was obtained.--

Please replace the paragraph beginning on page 58, lines 8-18 with the following paragraph.

--To a suspension of N-(piperidin-4-yl)-4-fluorobenzamide (556 mg) in dichloromethane (6 ml) were added cyclopropanecarboxylic acid (0.20 ml), 1-hydroxybenzotriazole (338 mg) and 1-[etyl]ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (480 mg) at ambient temperature. After stirring for 21 hours, the mixture was diluted with dichloromethane, and washed with water, saturated aqueous sodium hydrogen carbonate, and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. After crystallization from diisopropyl ether, N-(1-

cyclopropylcarbonylpiperidin-4-yl)-4-[fluorobenzamide]fluorobenzamide (627 mg) was obtained.--

Please replace the paragraph on page 61, lines 3-13 with the following paragraph.

--To a solution of N-(1-acetylpiperidin-4-yl)-4-fluorobenzamide (529 mg) in N,N-dimethylformamide (5 ml) was added sodium hydride (0.1 g). After stirring for 45 minutes, methyl iodide (623 ml) was added to the solution. After stirring for 45 minutes, the mixture was diluted with ethyl acetate (100 ml) and water (50 ml). An organic phase was separated, and washed with water and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. After trituration with [diisopropyl] diisopropyl ether, N-(1-acetylpiperidin-4-yl)-N-methyl-4-fluorobenzamide (248 mg) was obtained.--

Please replace the paragraph on page 61, lines 19-31 with the following paragraph.

--A suspension of 1-acetylpiperazine (0.627 g), 2-chloro-4'-fluoroacetophenone (0.844 g), and potassium hydrogen carbonate (0.735 g) in acetonitrile (12 ml) was stirred at ambient temperature for 3 days. After removal of the solid by filtration, the filtrate was evaporated under reduced pressure to give a residue, which was chromatographed on silica gel (100 ml) eluting with 0%-5% methanol in dichloromethane. The objective compound of the free form was taken up into ethyl acetate (2 ml) and to the solution was added a solution of hydrogen chloride in ethyl acetate (4N, 2 ml). The resulting precipitate was collected by filtration, washed with [diisopropyl] diisopropyl ether, and dried in vacuo to give 1-acetyl-4-(4-fluorophenylcarbonylmethyl)piperazine [hydrochloride] hydrochloride (1.47 g).--